REMARKS

Claims 1-17 are pending in this application. Claim 1 is currently amended. Support for the amendment can be found throughout the application as filed, e.g., at Fig. 1. No new matter has been added.

Interview Summary

Applicants thank Examiner Joike for holding a telephonic interview with the undersigned on June 10, 2010. The Examiner and the undersigned discussed the present rejection for alleged obviousness, specifically with regard to the Walhout et al. and Fields et al. references and the possibility of presenting evidence of secondary considerations.

Claim Rejections - 35 USC § 103

Claims 1-7 and 11-13 were rejected as being allegedly unpatentable over Walhout et al. (Methods Enzymol., 328:575-592, 2000) in view of Fields et al. (Nature, 340:245-246,1989) and further in view of Sugawara et al. (Med. Sci. Monit., 8:BR431-438, 2002). Applicants respectfully traverse the rejection.

At page 5, the Office action states: "Walhout et al teaches a vector with an ORF of at least 250 bp and flanked by lambda recombination sites transformed into a yeast cell. The vector can be integrated into the genome (p. 579)." The Office action concedes that "the reference does not explicitly state the vectors are integrated into a yeast genome," but alleges that "it is inherent that they are." Applicants respectfully submit that Walhout et al. does not disclose, explicitly or inherently, that the vector can be integrated into the genome of a yeast or mammalian cell. Walhout et al. discloses that the vector contains sites for integration phage lambda into and from the *E. coli* genome. Based on this disclosure, the Office action states that "It follows that vectors with lambda recombination sites that are transformed into yeast will also integrate." However, the integration reactions require elements not naturally present in yeast or mammalian cells, including the attB site located on the *E. coli* genome, the phage protein integrase (Int), and the bacterial protein integration host factor (IHF). Walhout et al., pages 579-580. Further, although

Walhout et al. uses the lambda recombination sites for integration of ORFs into plasmids *in vitro* (see Fig. 2B-D), these ORFs are never integrated into the genome of an organism. For a finding of inherency, it must be established that the allegedly inherent characteristic is necessarily present in prior art disclosure See MPEP § 2112 IV. There is no explicit or inherent disclosure in Walhout of integration of a vector comprising lambda recombination sites into a yeast genome. Therefore, Walhout et al. neither teaches nor suggests integration of a bait element or any other nucleic acid into the genome of a yeast or mammalian cell.

Fields et al. does not remedy the deficiencies of Walhout et al. At page 5, the Office action states: "Fields et al. teach assessing activation of a reporter gene when the fusion protein of a DBD and TAD bind to the binding element (UAS_G). See figure 1." However, this is inaccurate. The only protein disclosed by Fields et al that contains both a DBD (DNA binding domain) and TAD (transcription activation domain) is the native GAL4 protein. See Fig. 1a. The fusion proteins disclosed include either a DBD or a TAD, but not both. See Fig. 1b. This arrangement allows for detection of detecting protein-protein interactions, as transcriptional activity only occurs when the DBD fusion protein and the TAD fusion protein interact. See Fig. 1c. However, Fields et al. does not teach or suggest the detection of DNA-protein interactions. The Office action further states: "It would be obvious to substitute the ORF taught by Walhout et al with the bait element taught by Fields et al, because Walhout et al teach the use of a vector with a binding domain, and Fields et al use UAS_G, which is a binding domain." This statement is also inaccurate. UAS_G is not a binding domain (i.e., a portion of a protein that binds to a DNA element), but a DNA element which is bound by a protein. Further, Walhout et al. discloses the preparation of a vector with an ORF fused to a binding domain for detection of protein-protein interactions (two-hybrid), rather than DNA-protein interactions. It would not have been obvious to substitute ORF of Walhout et al. with the UAS_G disclosed in Fields et al. because the regions involved are used for divergent purposes. The ORF of Walhout et al. encodes a polypeptide and is used in fusion proteins to detect protein-protein interactions. The UAS_G disclosed in Fields et al. is a DNA element that is involved in activation of transcription. Substituting the UAS_G for the ORF of Walhout et al. would not have yielded a useful fusion

protein, as the UAS_G is not a coding sequence. Because the sequences have different functions, one skilled in the art would not have substituted one for the other. Additionally, because of the differences in function, the sizes of the ORFs disclosed in Walhout et al. cannot be used to meet the size limitation of the claimed bait element. The Office has provided no teaching or suggestion of a bait element of at least 250 base pairs.

Sugawara et al. likewise does not remedy the deficiencies of Walhout et al. and Fields et al. for several reasons. Sugawara et al. generally discusses the use of a one-hybrid system to detect endocrine-disrupting compounds with the yeast strain YM4271. In this method, Sugawara et al. uses three tandem copies of an estrogen response element (ERE) reporter construct. Thus, even if the EREs were each considered a "bait element" as claimed, Sugawara's three EREs, do not teach or suggest use of a *single copy of a bait element* as claimed. In addition, each ERE is about 30 bp (see page BR432, second column, "Plasmid Constructs"). Altogether, the three tandem copies of the ERE would only come to about 90 bp, therefore Sugawara et al. does not teach or suggest a bait element having *at least 250 base pairs* as presently claimed. Further, Sugawara et al. fails to disclose or suggest the use of *lambda recombination sites*.

As discussed above, none of Walhout et al., Fields et al., or Sugawara et al. describes a yeast or mammalian cell whose genome includes one or more integrated bait-reporter constructs, wherein each of the one or more bait-reporter constructs includes (a) a single copy of a bait element having at least 250 base pairs flanked by lambda recombination sites, wherein the bait element comprises at least 250 base pairs, and (b) a reporter gene. The ORFs discussed in Walhout et al. are not functionally equivalent to the bait element recited in the claims, and none of the references teaches or suggests a yeast or mammalian cell having an integrated bait-reporter construct with a bait element flanked by lambda recombination sites. In view of the errors in the factual findings with regard to the references, the Office's combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest every element of the claims, and the Office has failed to establish a *prima facie* case of obviousness.

Additionally, the claimed invention provides advantages that are not taught or suggested by the cited art. For example, only one copy of the DNA bait element is required (cf. Sugawara

et al.), and the methods can be used with bait elements of 250 bp in length or greater. These advantages make it especially suitable for high throughput screening to identify proteins that bind to promoter regions or *vice versa*.

Based on the above arguments, applicants submit that the claims are therefore patentable over the combination of Walhout et al. in view of Fields et al. and Sugawara et al.. Applicants respectfully request reconsideration and withdrawal of the rejection for alleged obviousness.

Claim 8 was rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of Luo et al. As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. Luo et al. does not remedy the deficiencies of Walhout et al., Fields et al., and Sugawara et al. Luo et al. discloses a mammalian two hybrid system to detect protein-protein interactions. This system uses three plasmids, two of which express the interacting fusion proteins and the third containing a reporter construct. Luo et al. does not teach or suggest the detection of DNA-protein interactions, a yeast or mammalian cell with a bait-reporter construct integrated into its genome, or a bait element flanked by lambda recombination sites. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and Luo et al. fails to teach or suggest every element of the claims, and Applicants request reconsideration and withdrawal of the rejection.

Claims 9 and 10 were rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of Chalfie et al. As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims, and Chalfie et al. does not remedy these deficiencies. Chalfie et al. describes the use of GFP as a transcriptional expression marker. However, Chalfie et al. does not teach or suggest the detection of DNA-protein interactions or a bait-reporter construct of any sort. Therefore, the combination of Walhout et al., Fields et al.,

Sugawara et al., and Chalfie et al. fails to teach or suggest every element of the claims, and Applicants request reconsideration and withdrawal of the rejection.

Claim 14 was rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of Cost et al. As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. Cost et al. does not remedy these deficiencies. While Cost et al. describes the use of MET15 as a reporter, it does not teach or suggest the detection of DNA-protein interactions or a bait-reporter construct of any sort. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and Cost et al. fails to teach or suggest every element of the claims, and Applicants request reconsideration and withdrawal of the rejection.

Claims 15 and 16 were rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of US 5,965,368 (the '368 patent). As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. The '368 patent does not remedy these deficiencies. The '368 patent generally discloses methods for identifying molecular interactions. According to the abstract of the '368 patent, "[a]ll of the methods within the invention employ counter-selection and at least two hybrid molecules." The '368 patent does not teach or suggest the claimed methods, which use only one hybrid molecule (a fusion protein comprising an activation domain, wherein binding of the fusion protein to the DNA bait element is detected). Further, the '368 patent does not teach or suggest a yeast or mammalian cell whose genome includes one or more integrated bait-reporter constructs, wherein each of the one or more bait-reporter constructs includes (a) a single copy of a bait element having at least 250 base pairs flanked by lambda recombination sites, wherein the bait element comprises at least 250 base pairs and (b) a reporter gene. Therefore, the combination of Walhout et al., Fields et

al., Sugawara et al., and the '368 patent fails to teach or suggest every element of the claims, and Applicants request reconsideration and withdrawal of the rejection.

Claim 17 was rejected as allegedly unpatentable over Walhout et al., Fields et al., and Sugawara et al., as applied to claims 1-7 and 11-13, above, and further in view of US 5,525,490 (the '490 patent). As discussed above, the combination of Walhout et al., Fields et al., and Sugawara et al. fails to teach or suggest each element of the claims. The '490 patent does not remedy these deficiencies. The '490 patent generally teaches reverse two-hybrid systems to screen for molecules that can inhibit protein-protein interactions. The '490 patent does not teach or suggest the detection of DNA-protein interactions or a yeast or mammalian cell whose genome includes one or more integrated bait-reporter constructs, wherein each of the one or more bait-reporter constructs includes (a) a single copy of a bait element having at least 250 base pairs flanked by lambda recombination sites, wherein the bait element comprises at least 250 base pairs and (b) a reporter gene. Therefore, the combination of Walhout et al., Fields et al., Sugawara et al., and the '490 patent fails to teach or suggest every element of the claims, and Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the arguments presented herein, applicants submit that the pending claims are patentable and request early and favorable action thereon. If the Examiner feels it would further prosecution of the present case, she is invited to telephone the undersigned at (617) 521-7020.

Applicants do not concede any positions of the Office that are not expressly addressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This reply is being submitted with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-0232US1.

Respectfully submitted,

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